Version with Markings to Show Changes Made

In the Specification

Page 1, paragraph 3 (TWICE AMENDED)

However, because of the necessity of manual aspetic removal and recovery of the MC powder from the tray using a scraper after completion of freeze-drying, the conventional method has the drawbacks described below. (1) MC powder adhesion to the tray necessitates the removal of MC powder using a scraper at **the** time of its recovery. (2) Because **[it takes a]** scraping is conducted manually, and because **it takes a** relatively long time to recover the MC, the MC is exposed to the environment for an extended period of time, resulting in the constant risk of contamination with microorganisms etc., an aspect undesirable from the viewpoint of assurance of sterility. Also, because MC preparations need water content control, such long environmental exposure poses a risk from the viewpoint of

Page 2, paragraph 2 (AMENDED)

Against this background there has been a demand for the development of a production method for a solid sustained-release preparation that enables easy recovery of the solid sustained-release preparation after freeze-drying at high recovery rates, with short environmental exposure time and reduced risk for production and **[entry]** **introduction** of foreign substances.

Page 22, paragraph 2 (TWICE AMENDED)

When the freeze-drying container (shelf temperature) is maintained at 0° C or below (preferably, -40° C to 0° C, more preferably, -20° C to 0° C, further preferably, -10° C to 0° C),

the temperature is maintained for more than about 0.1 hours, preferably for about 1 hour to about 500 hours, more preferably for about 5 hours to about 100 hours in order to **[completing]** **complete** the sublimation of frozen water in the freeze-drying container.

Page 25, paragraph 2 (AMENDED)

(3) Because of obviation of the necessity of MC powders removal using a scraper, there is no risk of production and **[entry]** **introduction** of foreign substances due to friction between the tray and scraper.

Page 28, paragraph 2 (AMENDED)

More specifically, when an LH-RH antagonist represented by general formula [Ia] or an LH-RH agonist represented by general formula [Ib], as described above, is used as the biologically active peptide, the sustained-release preparation (solid) of the present invention can be used as therapeutic/prophylactic agents for hormone-dependent diseases, including prostatic cancer, prostatic hypertrophy, endometriosis, hysteromyoma, metrofibroma, precocious puberty, breast cancer, gallbladder cancer, uterine cervical cancer, chronic lymphatic leukemia, chronic myelocytic leukemia, colorectal cancer, gastritis, Hodgkin's disease, malignant melanoma, metastatic/multiple myeloma, non-Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, digestive ulcer, systemic fungal infection, small cell lung cancer, cardiac valvular disease, mastopathy, polycystic ovary, infertility, chronic anovulation, induction of appropriate ovulation in women, acnes, amenorrhea (e.g. secondary amenorrhea), cystic diseases of ovary and breast (including polycystic ovary), gynecologic cancers, ovarian hyperandrogenemia and hypertrichosis, AIDS due to T cell production mediated via thymus blastogenesis, and male **[infertilization]** **sterilization** for treatment of male sexual crime offenders, as drugs for contraception and mitigation of symptoms in premenstrual syndrome (PMS), as agents for in

vitro fertilization (IVF), etc., and in particular, as therapeutic/prophylactic agents for prostatic cancer, prostatic hypertrophy, endometriosis, hysteromyoma, metrofibroma, precocious puberty etc., and as contraceptives.

In the Claims

1. (AMENDED) A method for producing a solid sustained-release **microsphere** preparation, which comprises freeze-drying a sustained-release **microsphere** preparation in a freeze-drying container of which the inner face is partially or wholly coated with an ice layer or water-repelling base material.

2. (AMENDED) A method for producing a solid sustained-release **microsphere** preparation, which comprises freeze-drying a sustained-release **microsphere** preparation in a freeze-drying container of which the inner face is partially or wholly coated with a water-repelling base material, and the coated inner face is further partially or wholly coated with an ice layer.

8. (AMENDED) The method according to claim 1 or 2 **[which comprises completing the sublimation of frozen water in the freeze-drying container under reduced condition that the temperature in the freeze-drying container]** wherein sublimation is at 0°C or below.

9. (AMENDED) The method according to claim **[3]** 1 wherein said **[sustained-release preparation is a]** microsphere is a microcapsule.

10. (AMENDED) The method according to claim **[4]** 2 wherein said **[sustained-release**

preparation is a] microsphere **<u>is a microcapsule</u>**.

REMARKS

I. Amendments

Claims 1, 2, 8, 9 and 10 have been amended, claims 7, 11 and 12 have been canceled and new claims 13-22 have been added.

Typographical and grammatical errors have also been corrected throughout the specification.

This amendment adds no new matter to the specification. Support for this amendment is found in the specification and claims as filed. Specifically, support for new independent claim 13 may be found *inter alia* at page 19, line 5- page 22, line 21; support for new independent claim 20 may be found *inter alia* at page 22, line 22 – page 24, line 10 and support for new independent claim 14 may be found *inter alia* at page 24, lines 13-29. New claims 15-19, 21, 22 dependent upon claims 13, 14 or 20 have also been added. These claims have been added to define the invention in accordance with U.S. practice.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

No change of inventorship is necessitated by this amendment.

II. Discussion of the Rejection under 35 U.S.C. Sec. 102(b)

Claims 1, 3-5 and 7-12 have been rejected under 35 U.S.C. Sec. 102(b) as being unpatentable over Ueda *et al.* (EP 0 394 050 A2).

By this amendment, claim 1 has been amended to indicate that the preparation is a microsphere preparation. Microsphere preparations are not disclosed in the cited reference.

Moreover, new claims 13-22 have been added. Applicants submit that their invention, as set forth in claims 13-22 is not anticipated by the cited reference.

Claims 3-5, 8 and 9 depend upon claim 1. Claims 7, 11 and 12 have been cancelled. Claim 10, as amended, depends upon independent claim 2. Applicants submit that these more specific dependent claims are also not anticipated by the cited reference. Therefore, Applicants respectfully request withdrawal of the Sec. 102 (b) rejection.

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Gail L. Winokur

Printed Name: Gail L. Winokur

III. Discussion of the Rejection under 35 U.S.C. Sec. 103(a)

Claims 1-12 have been rejected under 35 U.S.C. Sec. 103(a) as being unpatentable over Ueda *et al.* (EP 0 394 050 A2).

By this amendment, claims 1 and 2 have been amended to indicate that the preparation is a microsphere preparation. Microsphere preparations are not taught or suggested by the cited reference.

Moreover, new claims 13-22 have been added. Applicants submit that their invention, as set forth in claims 13-22 is not rendered obvious by the cited reference.

Claims 3-6 and 8-10 depend upon claims 1 or 2. Claims 7, 11 and 12 have been cancelled. Applicants submit that these more specific dependent claims are also not rendered obvious by the cited reference. Therefore, Applicants respectfully request withdrawal of the Sec. 103(a) rejection.

IV. Conclusion

Reconsideration of the claims as amended and allowance is requested. Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, she is respectfully requested to call Applicants' attorney at (847) 383-3391.

Respectfully submitted,

Dated: November 27, 2001

Elaine M Ramesh

(847) 383-3391
(847) 383-3372

Elaine M. Ramesh, Ph.D., Reg. No. 43,032
Mark Chao, Ph.D., Reg. No. 37,293
Attorney for Applicants
Customer No. 23,115

Takeda Pharmaceuticals North America, Inc.
Intellectual Property Department
Suite 500, 475 Half Day Road
Lincolnshire, IL 60069 USA